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| EXAMINER |
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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/668,453 | CURIEL, DAVID T. | |
| | Examiner | Art Unit | |
| | Quang Nguyen, Ph.D. | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *30 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *22-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/11/04; 10/12/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Claims 1-27 are pending in the present application.

Applicant's election with traverse of Group I (Claims 1-21) in the reply filed on 9/30/04 is acknowledged. The traversal is on the ground(s) that both Groups I and II are directed to methods of using modified adenoviruses and that any search for the methods of the Group I claims will certainly encompass references for the methods of the Group II claims. Therefore, it would not place an unnecessary burden on the Examiner to search and examine both groups together. Applicants further argue that the present restriction would result in inefficiencies and unnecessary expenditures by both the Applicants and PTO, as well as extreme prejudice to Applicants because of a shortened patent term may result in any divisional applications filed in view of GATT. This is not found persuasive for the following reasons:

The methods of Groups I and II have different starting materials, different desired end-results, and therefore different technical considerations for achieving these different desired end-results. For example, none of the methods of Group I require the step of detecting fluorescence to monitor the replication and distribution of adenoviral vectors **or** constructing an adenoviral vector that expresses a fusion protein comprising an adenoviral structural protein (please note that this includes but not limited to adenoviral capsid proteins) and a fluorescent tag as required by the method of Group II. Therefore, a search for the invention of Group I would not reveal references related to the invention of Group II. It would also be unduly burdensome for the examiner to perform a complete search of the defined areas in both the patent and non-patent

literature, **and** consider the patentability of both the inventions (different desired outcomes for methods of Groups I-II) in a single application.

With respect to the issues of inefficiencies and unnecessary expenditures by both the Applicants and PTO as well as the shortened patent term, these issues are not relevant to the restriction requirements under 35 U.S.C. 121.

The requirement is still deemed proper and is therefore made FINAL.

Claims 22-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 9/30/04.

Accordingly, claims 1-21 are examined on the merits herein.

## *Claim Objections*

Claims 9 and 20 are objected to because the term "CAR-independent" should be spelled out in full at the first occurrence of the term. Appropriate correction is required.

## *Priority*

Upon review of the specifications of U.S Serial No. 10/424,409, filed on 4/28/03; U.S. Serial No. 09,668,791, filed on 9/22/2000, now US Patent 6,555,368; and the provisional application 60/156,104, filed on 9/24/1999, it is determined that the instant examined claims 1-21 are entitled to the priority date of 9/24/1999.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

(a) A method of increasing the ability of an adenovirus to transduce a specific cell type relative to an unmodified adenovirus, comprising the step of modifying a gene encoding an adenoviral capsid protein by introducing a DNA sequence encoding a small peptide into said gene or by introducing a DNA sequence encoding a single chain antibody into either the 5' end of the minor capsid protein pIIIa gene or the 3' end of the minor capsid protein pIX gene;

(b) A method of killing tumor cells in an individual, said method comprising the steps of:

injecting directly to said tumor cells an effective amount of recombinant adenoviruses comprising a therapeutic gene that converts a non-toxic compound to a toxic compound and a gene encoding a pIIIa protein or a pIX protein modified by introducing a single chain antibody into the N-terminus of said pIIIa protein or the C-terminus of said pIX protein; and

treating said individual with an effective amount of said non-toxic compound;

does not reasonably provide enablement for a method of increasing the ability of an adenovirus to transduce a specific cell type by other modifications of a gene

encoding an adenoviral capsid protein; or a method of killing tumor cells in an individual comprising the step of administering to said individual an effective amount of recombinant adenoviruses comprising a therapeutic gene that converts a non-toxic compound to a toxic compound and a gene encoding any other adenoviral capsid protein modified by introducing a single chain antibody into said protein at any site and/or by any route of delivery. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

Claims 1-11 are drawn to a method of increasing the ability of an adenovirus to transduce a specific cell type, comprising the step of modifying a gene encoding an adenoviral capsid protein, wherein said modification increases the ability of said adenovirus to transduce a specific cell type; the same method with various limitations recited in the dependent claims.

Claims 12-21 are directed to a method of killing tumor cells in an individual comprising the steps of: administering to said individual an effective amount of recombinant adenoviruses comprising a therapeutic gene that converts a non-toxic

compound to a toxic compound and a gene encoding an adenoviral capsid protein modified by introducing a single chain antibody into said protein; and treating said individual with said non-toxic compound; the same method with various limitations recited in the dependent claims.

With respect to the elected invention, the specification teaches by exemplification showing the construction and preparation of a recombinant adenovirus vector comprising either an insert of 6-His coding sequence at the 5' end of a sequence encoding an adenoviral pIIIa minor capsid protein or a small 8-amino acid peptide Flag tag coding sequence at the 3' end of a sequence encoding an adenoviral pIX minor capsid protein. Applicants further noted that based on the elucidation that the pIX C-terminus is surface exposed, pIX has been exploited as a locale to incorporate heterologous peptides such as octapeptide, polylysine for retargeting purposes, as well as a single chain variable fragment (scFv) against the c-erbB-2 oncoprotein (see instant specification page 20, line 20 continues to line 7 of page 21). Additionally, the Declaration under 37 C.F.R. 1.132 filed on 4/11/02 in the parent US application 09/668,791, now US patent 6,555,368, demonstrated that the above modified adenoviral vector incorporating anti-c-erbB-2 scFv possesses the ability to recognize c-erbB-2 receptor in addition to CAR, and confirming the targeting and binding of activities of the modified vector.

The above evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the instant broadly claimed invention for the reasons discussed below.

***1. The breadth of the claims***

Claims 1-11 are directed to a method of increasing the ability of an adenovirus to transduce any specific cell type (e.g., bronchial epithelial cells, small airway epithelial cells, macrophages, endothelial cells, smooth muscle cells) by modifying any gene encoding an adenoviral capsid protein (e.g., any major capsid proteins such as fiber, penton and hexon and any minor capsid proteins such as pIIIa, pIX and others) in any manner (e.g., introducing a small peptide, a single chain antibody or other complex structural ligands) as long as the modification results in an increased ability of the modified adenovirus to transduce a specific cell type. Additionally, claim 10 is directed to the same method wherein the adenovirus further comprises any additional modification to an adenovirus fiber knob, wherein the modification to the fiber knob ablates the native tropism of the modified adenovirus. As written, claims 2-5 are drawn to a method of increasing the ability of an adenovirus to transduce a specific cell type by introducing a single chain antibody into any gene encoding an adenoviral capsid protein.

Claims 12-21 are drawn to a method of killing tumor cells in an individual, comprising the steps of administering to said individual at any site by any route of delivery an effective amount of recombinant adenoviruses comprising a therapeutic gene that converts a non-toxic compound to a toxic compound and a gene encoding any adenoviral capsid protein (e.g., any major capsid proteins such as fiber, penton and hexon and any minor capsid proteins such as pIIIa, pIX and others) modified by introducing a single chain antibody into said protein; and treating said individual with

said non-toxic compound. Additionally, claim 21 is directed to the same method wherein the adenovirus further comprises any additional modification to an adenovirus fiber knob, wherein the modification to the fiber knob ablates the native tropism of the modified adenovirus.

***2. The state and unpredictability of the prior art***

At the effective filing date of the present application (09/24/1999), apart from the introduction of short non-native amino acid sequences into adenoviral coat fiber, hexon or penton proteins in modified adenoviral vectors that are more efficient than wild-type adenoviral vectors for cell entry (WO 97/20051; WO 99/36545; Wickham et al., US Patent 5,846,782; AB, IDS), virtually nothing was known on the introduction of any large physiological ligands or complex structural ligands or antibodies including single chain antibodies into any adenoviral capsid protein for cell-specific targeting. Regarding to the incorporation of heterologous ligands in the HI loop of an adenoviral fiber protein knob, Curiel (Ann. NY Acad. Sci., 886:158-171, 1999; see pages 167-168; AF, IDS) stated that "[t]he size constraints of ligand incorporation at this site are yet determined; therefore, incorporation of large ligands such as EGF and sFvs is currently investigated. However, it is likely that the sheer size of the sFv will require an alternate strategy such as complete replacement of the entire knob region. Ultimately, for true targeting to be achieved, modification to ablate native tropism will need to be addressed. It may be that incorporation of large ligands into the HI loop will simultaneously ablate native tropism by steric hindrance; however if this is not the case, further modification will be required....if complete replacement of the knob with a targeting and trimerization moiety

could be achieved, it would simultaneously ablate native tropism". Applicant has also stated in the present disclosure that "The inability to configure single chain antibodies at fiber, hexon and penton locales has indicated the need to examine the ability of single chain antibodies to be incorporated into alternate capsid proteins" (page 4, line 20 continues to line 2 of page 21).

Moreover, at the effective filing date of the present application it was also unclear in the art exactly how to ablate the native tropism of an adenovirus as evidenced by the statement of Curiel cited above. In a review of viral vector targeting, Peng et al. (Curr. Opin. Biotech. 10:454-475, 1999; AO, IDS) also stated that "[I]t is important to remember that re-targeted vectors may have more than one binding specificity, being capable of binding not only to the targeted molecule but also to the natural receptor that is recognized by the unmodified vector coat protein. Thus, there will be no substitute for empirical *in vivo* studies to determine how these binding modifications will influence vector localization (page 454, col. 2, last full paragraph). Additionally, Douglas et al. (Nature Biotech. 17:470-475, 1999; AI, IDS) stated that "Thus, to date it has not proven possible to employ genetic methods to engineer Ad vectors with specificity for a single target cell type. In addition to recognizing novel receptors, such vectors should also lack the ability to bind to the native primary Ad receptor. This could be accomplished by site-directed mutagenesis of the fiber knob domain to eliminate the cell-binding site or by complete deletion of the fiber knob. However, an important consequence of the ablation of native Ad tropism is that it will not be possible to exploit the native cellular entry pathway to propagate these vectors in standard packaging cell lines such as 293

and 911" (page 470, col. 2, last full paragraph). Several years after the effective filing date of the present application, even the ablation of coxsackie-adenovirus receptor CAR-binding or both CAR and αv integrin-binding is not sufficient to change the biodistribution of adenoviral vectors, particularly to the liver (Alemany et al., Gene therapy 8:1347-1353, 2001; Martin et al., Molecular therapy 8:485-494, 2003).

Furthermore, with respect to claims 2-5 virtually nothing was known in the prior art at the effective filing date of the present application on the introduction of any peptide or single chain antibody which is made up of amino acid residues into any gene which is composed of nucleotides for the modification of the gene, including one that encodes a capsid protein, for increasing the ability of an adenovirus to transduce a specific cell type.

With respect to claims 12-21, at the effective filing date of the present application (09/24/1999) vector targeting *in vivo* to targeted cells, tissues or organ was and continues to be unpredictable and inefficient. This is supported by numerous teachings available in the art. For example, Miller & Vile (FASEB 9:190-199, 1995; AM, IDS) reviewed the types of vectors available for *in vivo* gene therapy, and concluded that "Targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (Exp. Opin. Ther. Patents 8:53-69, 1998; AH, IDS) indicated that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain

also reviewed new techniques under experimentation in the art that show promise, but is currently even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma et al. (Nature 389:239-242,1997; AQ, IDS) reviewed various vectors known in the art for use in gene therapy and the problems which are associated with each and clearly indicated that resolution to *in vivo* vector targeting had not been achieved in the art (see the entire article). Verma et al. also discussed the role of the immune system in inhibiting an efficient targeting of viral vectors to desired target cells (see page 239, second and third columns of page 242). Even in 1999, Meng et al. (In Gene therapy of cancer; Chapter 1, pages 3-20, 1999; AL, IDS) noted there are several barriers associated with an intravascular delivery of target genes for cancer gene therapy. These include, the dilution of the gene delivery vehicle such that only a small portion may ultimate reach the desired target organ or cell; the elicitation of powerful adverse host immune response; tropism for organs such as liver for adenovirus should the intended organ is elsewhere; and the traverse of the recombinant viral vector against the endothelial wall and travel against pressures within an expanding tumor mass (see section titled "Route of administration" on pages 5-6). Dang et al. (Clin. Cancer Res. 5:471-474, 1999, see the entire article, particularly page 471, col. 1, first paragraph; AG, IDS) also noted that there are many factors known to limit the effectiveness of gene therapy, among which are the lack of optimal vectors, the lack of a long-term and stable transgene expression *in vivo*, the adverse host immunological responses to the vectors and more importantly the lack of an efficient gene delivery to target tissues or cells.

***3. The amount of direction or guidance provided***

Apart from the exemplification showing the construction and preparation of a recombinant adenovirus vector comprising either an insert of 6-His coding sequence at the 5' end of a sequence encoding an adenoviral pIIIa minor capsid protein or a small 8-amino acid peptide Flag tag coding sequence at the 3' end of a sequence encoding an adenoviral pIX minor capsid protein, as well as a successful demonstration that a single chain variable fragment (scFv) against the c-erbB-2 oncoprotein could also be incorporated into the C-terminus of the pIX minor capsid protein (modification to the 3' end of the pIX gene), the instant specification fails to provide sufficient guidance for a skilled artisan on how to introduce any large and/or complex structural ligand such as a single chain antibody into an adenoviral fiber, hexon or penton capsid protein for increasing the ability of a modified adenovirus to transduce a specific cell type. There is an absence of any guidance on how to overcome the known structural constraints which limit the extent to which large heterologous sequences can be introduced into adenoviral fiber, hexon and penton capsid proteins, such that a functional and mature recombinant adenovirus comprising the genetically modified capsid protein could be attained, especially in light of the state of the prior art discussed above. The present disclosure also fails to provide any teachings regarding to which modification(s) on which other minor capsid gene(s) at which domain(s) to increase the ability of the modified adenovirus to transduce any specific cell type or to administer the modified adenovirus into an individual for killing tumor cells. Nor does the instant specification provide sufficient guidance regarding to which amino acid(s) of any adenoviral capsid

protein (e.g., major and minor capsid proteins) to be substituted and/or deleted at which position(s) and in which combination(s) for the insertion of any ligand including a single-chain antibody, such that the resulting genetically modified adenovirus has an increased ability to transduce a specific cell type as contemplated by Applicant. There is a high degree of unpredictability associated with the make and use of the claimed embodiment as evidenced at least by the teachings of Peng et al. (Curr. Opin. Biotech. 10:454-475, 1999; AO, IDS) and Douglas et al. (Nature Biotech. 17:470-475, 1999). It is further noted that only the C-terminal end of the pIX protein points outward or constitutes the surface domain (Akalu et al, J. Virol. 73:6182-6187, 1999), such that the extremity could be modified without altering the overall structural properties of the pIX protein which is known to participate in the stability of the viral icosahedron and other adenenoviral functions as taught by Rosa-Calatrava et al. (J. Virol. 75:7131-7141, 2001; AK, IDS), and that a heterologous ligand can be introduced at the N-terminus of the pIIIa minor capsid protein, and not at any other regions or domains of the pIX and pIIIa minor capsid proteins.

An embodiment of the instant claimed invention (see claims 10 and 21) encompasses the utilization of a modified recombinant adenovirus further comprising an additional modification to an adenovirus fiber knob, wherein the modification to said fiber knob ablates the native tropism of the adenovirus. The present disclosure fails to provide any guidance for one skilled in the art on any modification of an adenoviral fiber knob that results in the ablation of the native tropism in either *in vitro* or *in vivo*. More importantly, there is no evidence of record in the present disclosure or in the prior art at

the effective filing date of this application (9/24/1999) indicating that even with a complete deletion of the fiber knob, the native tropism of the modified adenovirus would be ablated. Furthermore, Douglas et al. (Nature Biotech. 17:470-475, 1999) noted that the precise location to carry out mutagenesis of the fiber knob to ablate the native fiber receptor-binding site was unknown at the effective filing date of the present application (page 473, col. 1, middle of the first paragraph). Even several years after the effective filing date of the present application, the ablation of coxsackie-adenovirus receptor CAR-binding or both CAR and αv integrin-binding has been demonstrated to be insufficient to change the biodistribution of adenoviral vectors, particularly to the liver (Alemany et al., Gene therapy 8:1347-1353, 2001; Martin et al., Molecular therapy 8:485-494, 2003).

With respect to claims 2-5, the instant specification fails to provide any guidance for a skilled artisan in the art how to modify any gene encoding an adenoviral capsid protein by introducing into said gene a single chain antibody, rather than a DNA sequence encoding a single chain antibody into said gene which is a conventional means in the art. Since the prior art as discussed above does not provide such guidance, it is incumbent upon the present application to do so. With the lack of sufficient guidance provided by the present disclosure, it would have required undue experimentation for a skilled artisan to make and use the methods as claimed.

The instant specification also fails to provide sufficient guidance for a skilled artisan on how to overcome the unpredictability of vector targeting *in vivo* known in the art as discussed above, such that an efficient delivering of a therapeutic gene that

converts a non-toxic compound to a toxic compound to tumor cells could be achieved by any route of delivery and/or at any site using the modified recombinant adenovirus of the presently claimed invention to attain the desired therapeutic effect. Since the prior art at the effective filing date of the present application failed to provide such guidance, once again it is incumbent upon the instant disclosure to do so. With the lack of sufficient guidance provided by the present disclosure, it would have required undue experimentation for a skilled artisan to make and use the method of killing tumor cells in an individual as claimed.

The courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in the patent application (27 USPQ2d 1662 *Ex parte Maizel*.).

Accordingly, due to the lack of guidance provided by the specification regarding to the issues set forth above, the breadth of the claims, and the unpredictability of the capsid-modified recombinant adenovirus for cell targeting and gene therapy art, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "increasing the ability of an adenovirus" in claim 1 and its dependent claims is a relative term which renders the claim indefinite. The term "increasing the ability" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Increasing the ability of an adenovirus with respect to what? Therefore, the metes and bounds of the claims are not clearly determined.

## *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 6-9 and 11 are rejected under 35 U.S.C. 102(a) as being anticipated by Romanczuk et al. (WO 99/36545) as evidenced by Wickham et al. (U.S. Patent No. 5,846,782; IDS).

Romanczuk et al. teach the construction of recombinant adenoviral vectors having encoded modified capsid proteins which comprise heterologous peptide ligands (e.g., the RGD containing sequences, the SV40 nuclear localization signal) that improve and/or alter the infectious capability of the vectors for delivering transgene to epithelial target cells such as normal human bronchial epithelial cells or small airway epithelial cells (abstract and pages 8-11). Romanczuk et al. specifically teach that the peptide ligands can be inserted into the fiber, hexon, penton and protein IX proteins of an adenovirus, and the modified recombinant adenovirus may contain any combination of such modifications (page 10, lines 18-20). Additionally, the recombinant adenoviral vectors comprise nucleotide sequences coding for one or more transgenes such as, cystic fibrosis transmembrane regulator, dystrophin, p53, p21, HSV thymidine kinase among others (page 14, lines 11-25). Romanczuk et al. further disclose that direct delivery of the recombinant adenovirus to cancer cells in an individual to effect the killing of tumor cells (page 20, lines 13-17; page 19, lines 19-21 and page 14, lines 11-25). It is also apparent from the teachings of Romanczuk et al. that the modified capsid protein retains its native display profile because the modified adenovirus is still functional in delivering transgene to epithelial target cells (see examples). Furthermore, the modified adenoviruses containing heterologous RGD sequences in capsid proteins of Romanczuk et al. are also capable of exhibiting coxsackievirus-Ad receptor (CAR) independent gene transfer as evidenced by the teachings of Wickham et al. (U.S. Patent No. 5,846,782) which showed that the presence of non-native RGD motif in a

loop of the adenovirus fiber protein of modified adenoviruses can overcome the fiber-mediated block to adenoviral-mediated gene delivery (see example 11 and Figure 20).

Accordingly, Romanczuk et al. anticipate the instant claims.

Claims 1, 8-9 and 11 are rejected under 35 U.S.C. 102(e) as being anticipated by Wickham et al. (U.S. Patent No. 5,846,782; IDS).

Wickham et al. teach the preparation of a recombinant adenovirus contain a modified adenovirus fiber protein (an adenoviral capsid protein) comprising a constrained non-native short sequence of amino acids that allows the recombinant adenovirus an enhanced infectivity towards a specific cell type relative to a wild type adenovirus (col. 3, lines 45-61). Additionally, Wickham et al. disclose that the non-native amino acid sequence can be inserted into a loop of the knob of a chimeric adenoviral fiber protein, e.g., an adenoviral fiber protein that has Ad5 fiber shaft and Ad2 fiber knob (col. 10, lines 1-13 and Fig. 1). Wickham et al. further teach that the recombinant adenovirus can carry a therapeutic gene such as an HSV thymidine kinase gene whose expression renders cells selectively sensitive to the killing action of antiviral compounds including acyclovir, gancyclovir and FIAU (col. 14, lines 50-57). Wickham et al. specifically teach the killing of tumor cells by direct contacting tumor cells with the disclosed recombinant adenovirus comprising a DNA sequence encoding a discrete killing agent such as a cytotoxin or HSV thymidine kinase (col. 17, lines 2-17; col. 18, lines 23-48). Since the modified adenoviruses are functional, it is apparent that their modified fiber coat proteins must retain the native display profile. Additionally, the

presence of the non-native RGD motif or RKKK2 motif in a loop of the adenovirus fiber protein of modified adenoviruses overcomes the fiber-mediated block to adenoviral-mediated gene delivery (see examples 4, 11 and Figures 7, 20), indicating that the modified adenoviruses are also capable of exhibiting coxsackievirus-Ad receptor (CAR) independent gene transfer.

Accordingly, Wickham et al. anticipate the instant claims.

Claims 1 and 8-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Wickham et al. (J. Virol. 71:8221-8229, 1997).

Wickham et al. disclose a method of producing two Ad vectors which contain modifications to the Ad fiber coat protein that redirect virus binding to either αv integrin [AdZ.F (RGD)] or heparin sulfate [AdZ.F(pK7)] cellular receptors, with the AdZ.F (RGD) increases gene delivery to endothelial and smooth muscle cells expressing αv integrin and the AdZ.F(pK7) increases transduction in multiple cell types lacking high levels of Ad fiber receptor, including macrophage, endothelial, smooth muscle, fibroblasts and T cells (see abstract, Figures 1 and 5). Wickham et al. further teaches that AdZ.F(pK7) significantly increase gene transfer *in vivo* to vascular smooth muscle cells of the porcine iliac artery following balloon angioplasty. Since the modified adenoviruses are functional and that they are capable of increasing gene delivery to endothelial and smooth muscle cells expressing αv integrin and cell types lacking high levels of Ad fiber receptor such as macrophages, fibroblast, T cells, endothelial and smooth muscle cells; the modified fiber coat protein must retain its native display profile and the modified

adenoviruses are capable of exhibiting coxsackievirus-Ad receptor (CAR) independent gene transfer.

Accordingly, Wickham et al. anticipate the instant claims.

## *Double Patenting*

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-11 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 17-27 of copending Application No. 10/424,409. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

## *Conclusion*

***No claims are allowed.***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Irem Yucel, Ph.D., at (571) 272-0781.

**To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636; Central Fax No. (703) 872-9306.**

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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*Quang Nguyen, Ph.D.*